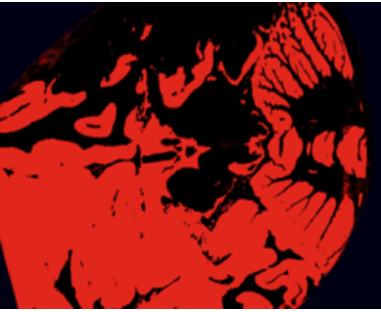

BRAINWEEK™ twenty 21 | Live Virtual Conference | MAY 7–9

A Delicate Balance: Prevention and Management of Acute Ischemic Stroke

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Disclosure

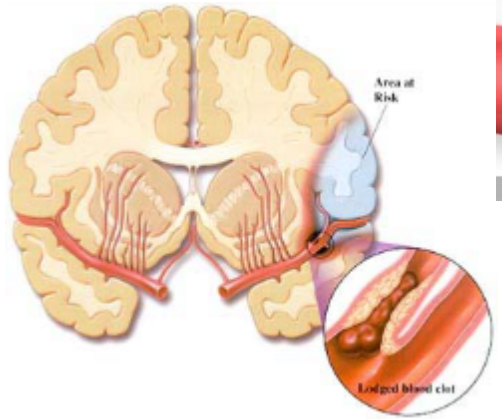
- The University of Florida has received research funding from Bristol-Myers Squibb and BMS-Pfizer/Roche Diagnostics for multicenter trials for which I am the local primary investigator.

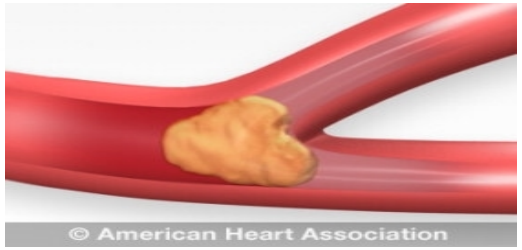
Learning Objectives

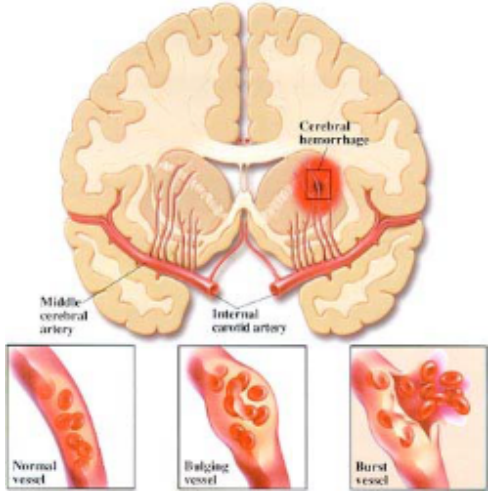
- Identify the treatment options for acute ischemic stroke
- List the factors that determine whether a patient is a candidate for acute thrombolysis and mechanical thrombectomy
- Recognize five causes of ischemic stroke
- Summarize recommendations for short-term and long-term secondary stroke prevention

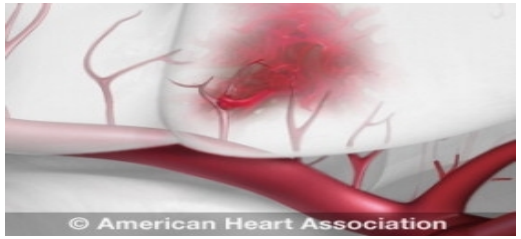
Types of Stroke

- Ischemic (87%)
  - Impaired blood flow due to vascular blockage
  - Transient ischemic attack (TIA): transient symptoms without evidence of infarction on MRI
- Hemorrhagic (13%)
  - Ruptured blood vessel
    - Intraparenchymal (10%)
    - Subarachnoid (3%)





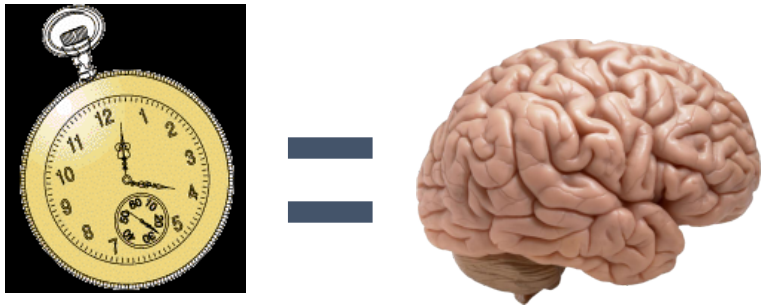




Acute Ischemic Stroke

1. Treatment
   - Reperfusion
     - Restore cerebral blood flow
   - Supportive care
     - Minimize damage
     - Prevent complications
2. Secondary prevention
   - Prevent recurrent stroke
     - Determination of stroke cause
     - Antithrombotic therapy

Time is Brain!



- Every minute increases the chance of stroke-related disability or death
- Timely medical intervention is crucial
- Estimated pace of brain function lost in an acute ischemic stroke:

Time	Neurons lost	Myelinated fibers lost*	Accelerated aging†
Every second	32,000	218 yards	8.7 hours
Every minute	1.9 million	7.5 miles	3.1 weeks
Every hour	120 million	447 miles	3.6 years
Every stroke	1.2 billion	4470 miles	36 years

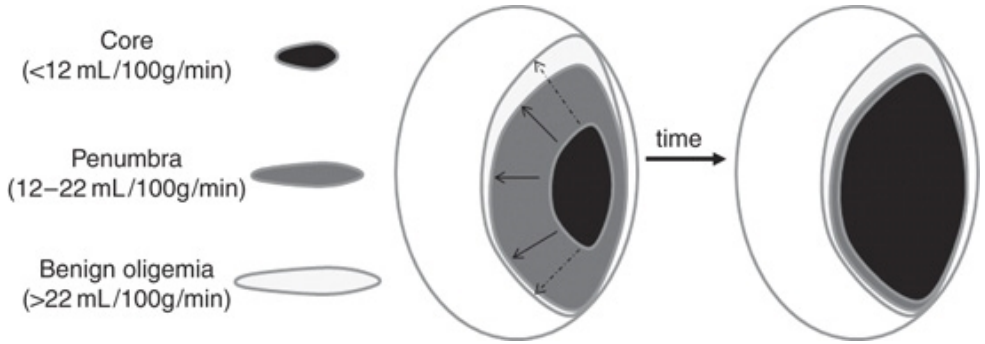
*Myelin fibers are nerve fibers wrapped in a protective myelin sheath

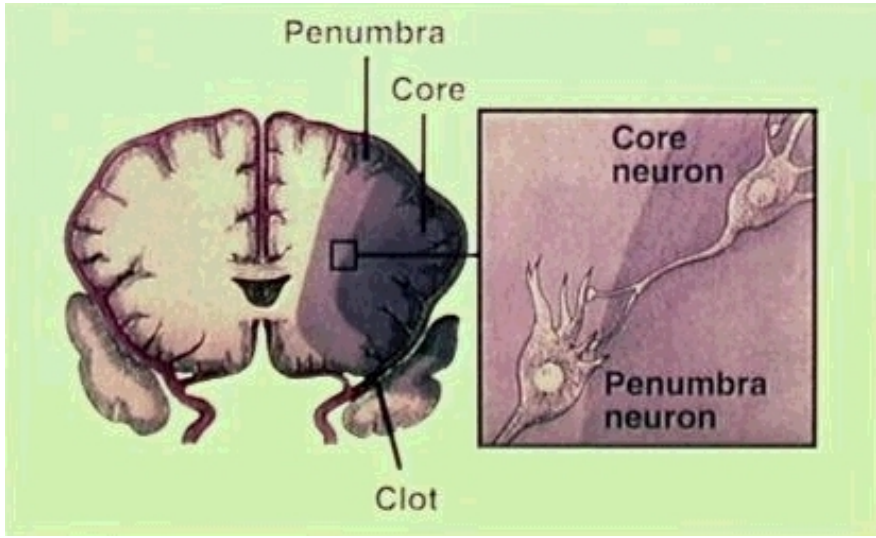
†Compared with normal aging, estimated at approximately 21 million neurons lost per year

Stroke 2006;37:263

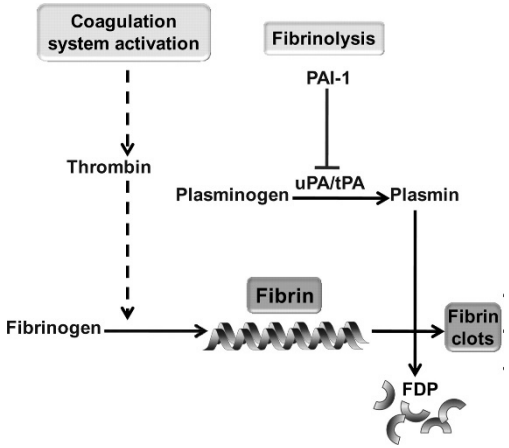
Treatment Goal: Save the Penumbra

- Core infarct = area permanently damaged by lack of blood flow
- Penumbra = area of salvageable tissue surrounding it
- Damage to the penumbra may be reduced if the flow of blood and oxygen to the tissue resumes
- Fast intervention is required!

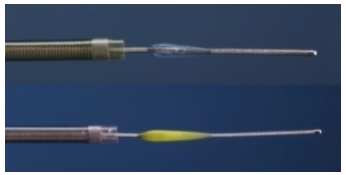


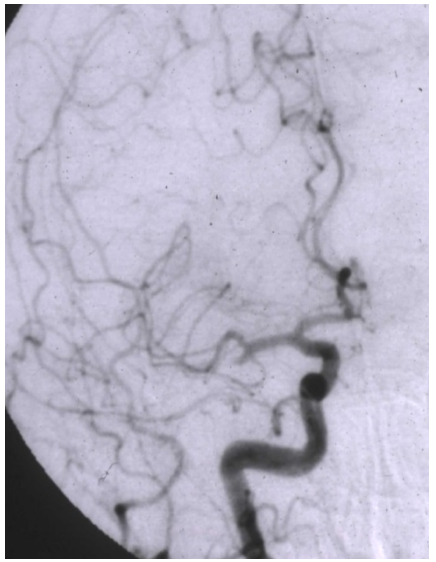


Reperfusion Options



- Systemic thrombolysis
  - Intravenous tissue plasminogen activator
- Endovascular
  - Mechanical thrombectomy





Decision-Making Elements

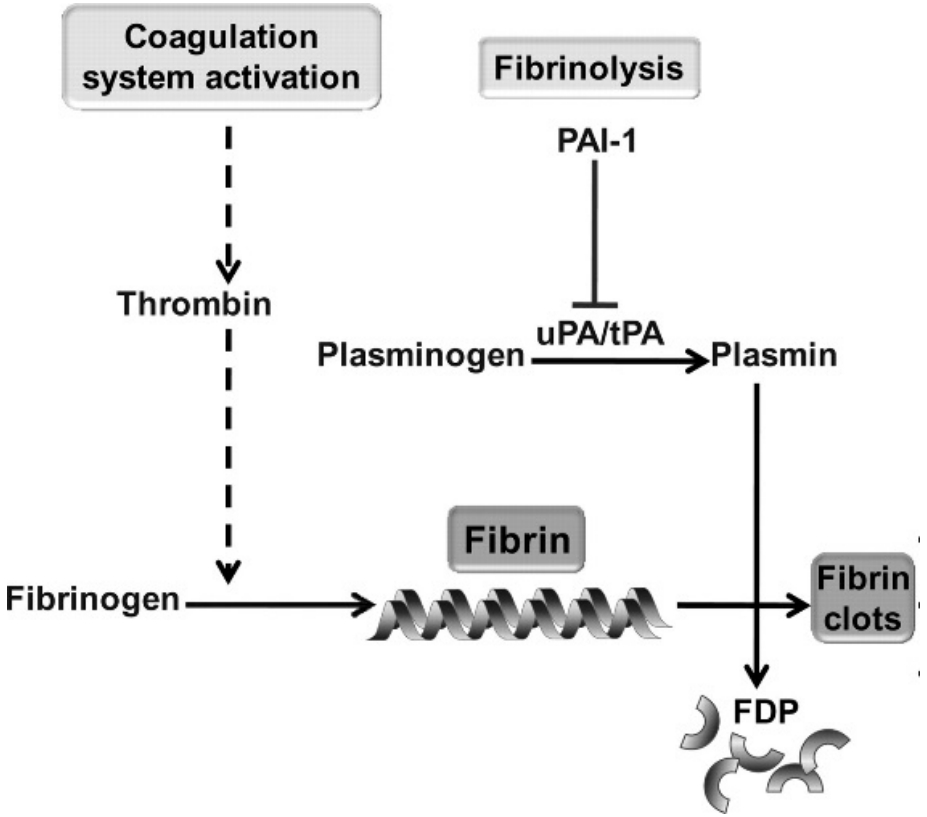
- Duration of symptoms
  - Specific time when the patient was last known well
- Nature/severity of symptoms
- History
  - Vascular risk factors
  - Prior stroke
  - Comorbidities (eg, trauma, cancer, recent surgery/bleeding)
- Focused medication history
  - Current use of antithrombotics
- Focused neurological exam
  - National Institute of Health Stroke Scale (NIHSS)
- CNS imaging

Neuroimaging – Head CT

- Diagnosis
  - Ischemic stroke
  - Hemorrhage
  - Stroke mimic
- Prognosis
  - Hypodensity = cytotoxic edema/core infarct
    - CT appears normal in early stroke
  - How large is the stroke?
  - Has the stroke already progressed too far for treatment?

Thrombolysis

- Alteplase (IV tPA)
  - Gold standard
- Time-based therapy
  - Administer within 4.5h of time last normal

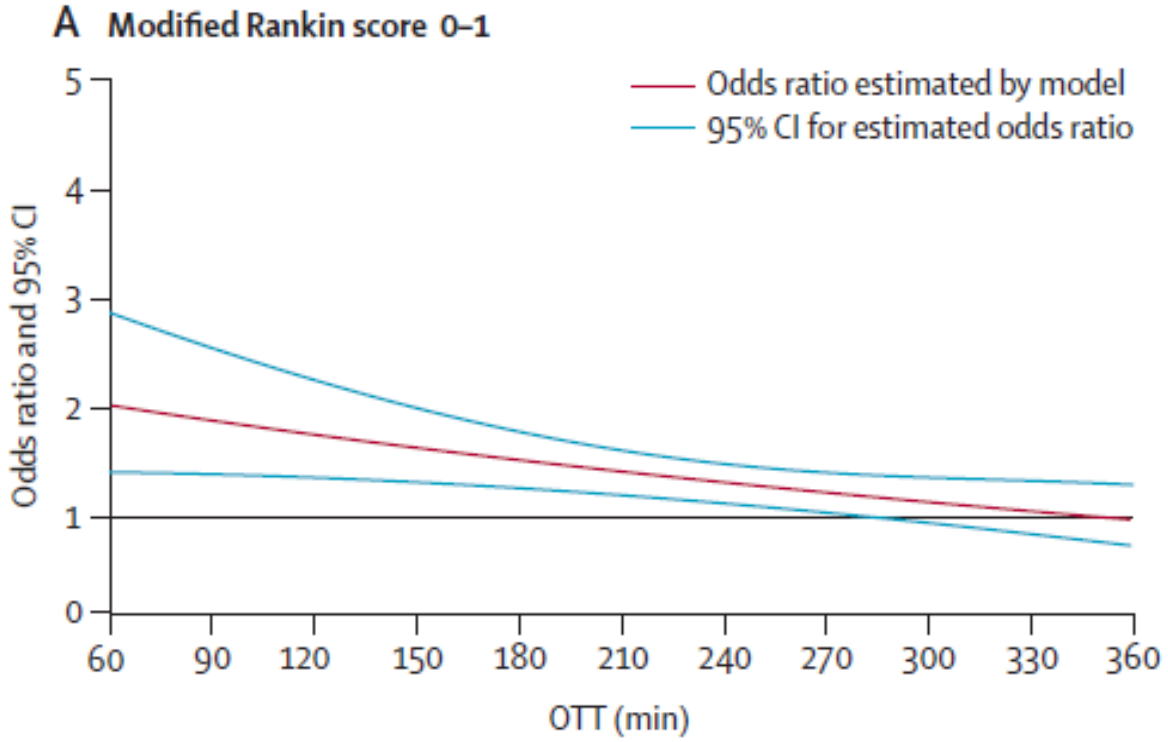


Thrombolytic Contraindications

Regular = absolute contraindication
Italics = relative contraindication
~~Strikeout~~ = historical contraindication

- Risk of CNS hemorrhage
  - >4.5 hours after time last normal
  - Visible evolving infarct in >1/3 MCA territory
  - Intracranial hemorrhage (current or *historical*)
  - *Recent neurosurgery, head trauma, or previous stroke – within 3 months*
  - *Intracranial neoplasm, arteriovenous malformation, or aneurysm*
  - *Uncontrolled hypertension at time of treatment*
    - > 185 mm Hg SBP or > 110 mm Hg DBP
- Risk of systemic hemorrhage
  - *GI/GU hemorrhage in past 21 days*
  - *Recent surgery (14 days)*
  - *Recent LP/arterial puncture at noncompressible site in past 7 days*
  - *Pregnancy*
  - Known bleeding diathesis:
    - INR > 1.7 or use of direct oral anticoagulants (DOACs)
    - Heparin with elevated aPTT
    - Platelet count <100,000
- Stroke mimics
  - ~~"Rapidly improving symptoms"~~ → treat if residual symptoms are disabling
  - ~~Seizure at onset~~ → treat if vascular cause suspected
  - ~~Glucose <60 or >400~~ → treat if vascular cause suspected

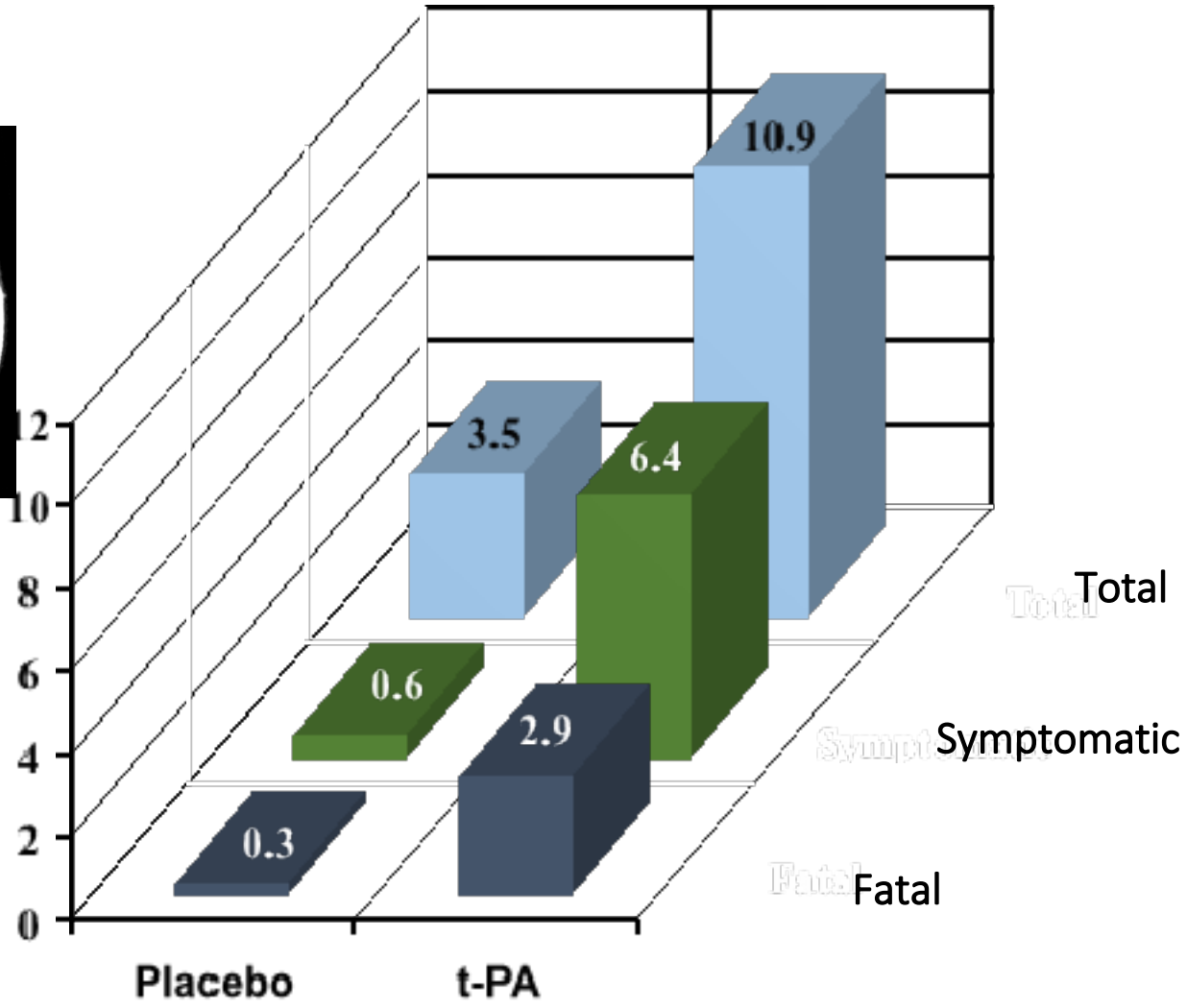
Odds of a Good Outcome After Thrombolysis Diminish With Time



Time interval	Number needed to treat	Absolute risk reduction
0 – 90 min	5	20%
91 – 180 min	9	11%
181 – 270 min	15	6.7%

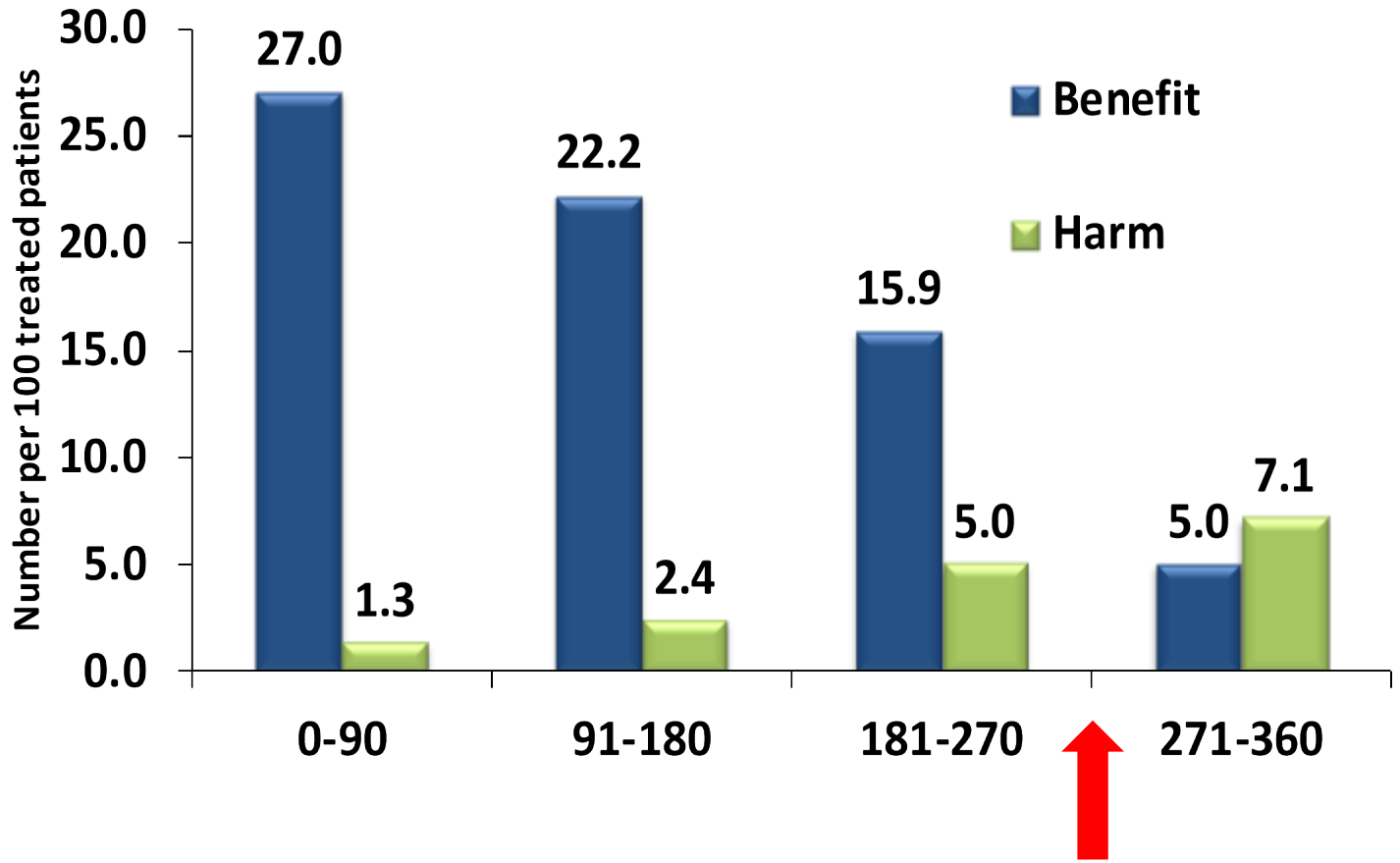
Lancet 2010; 375:1695

IV tPA complications: Hemorrhage



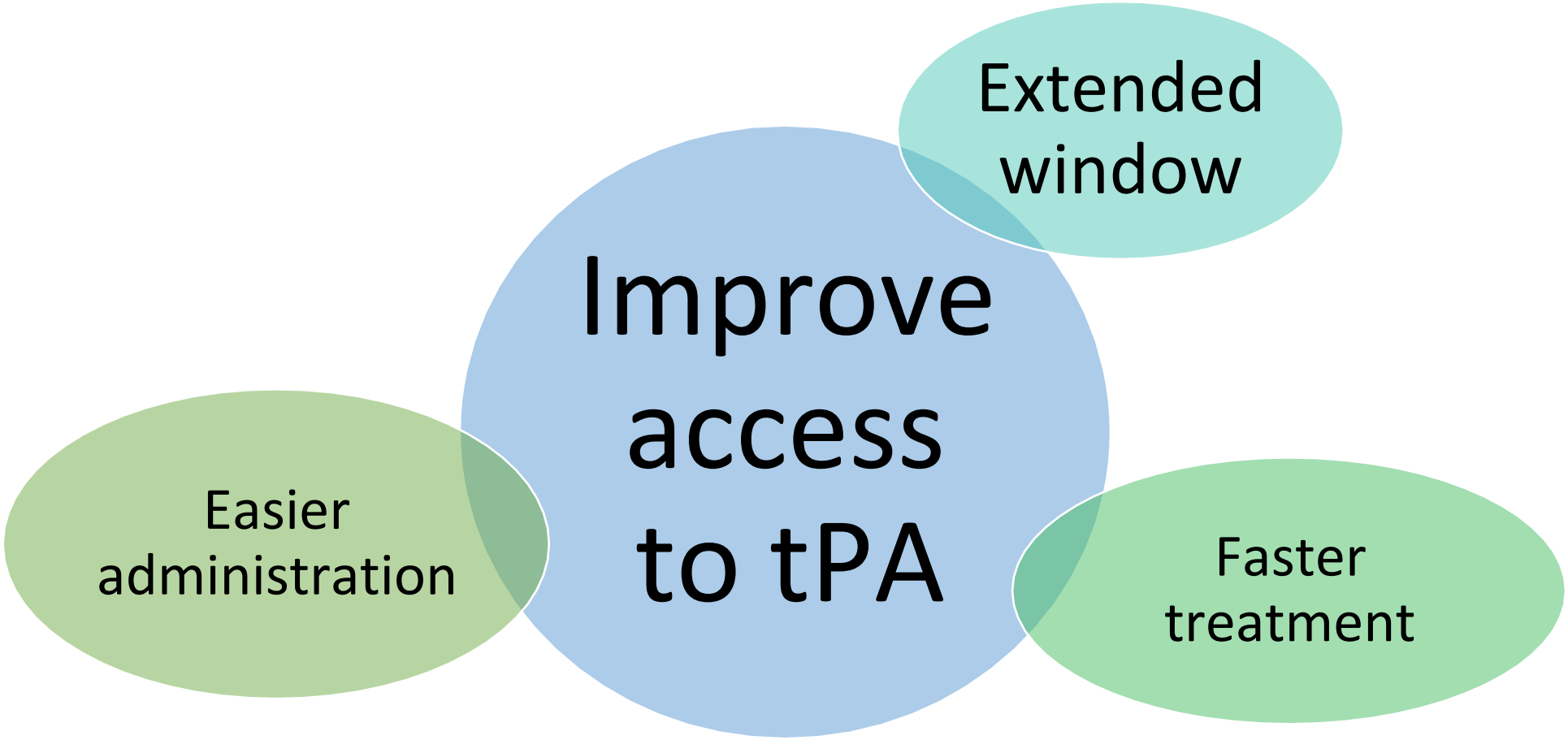
NEJM 1995;333:1581

Odds of Post-Thrombolysis Hemorrhage Increase with Time



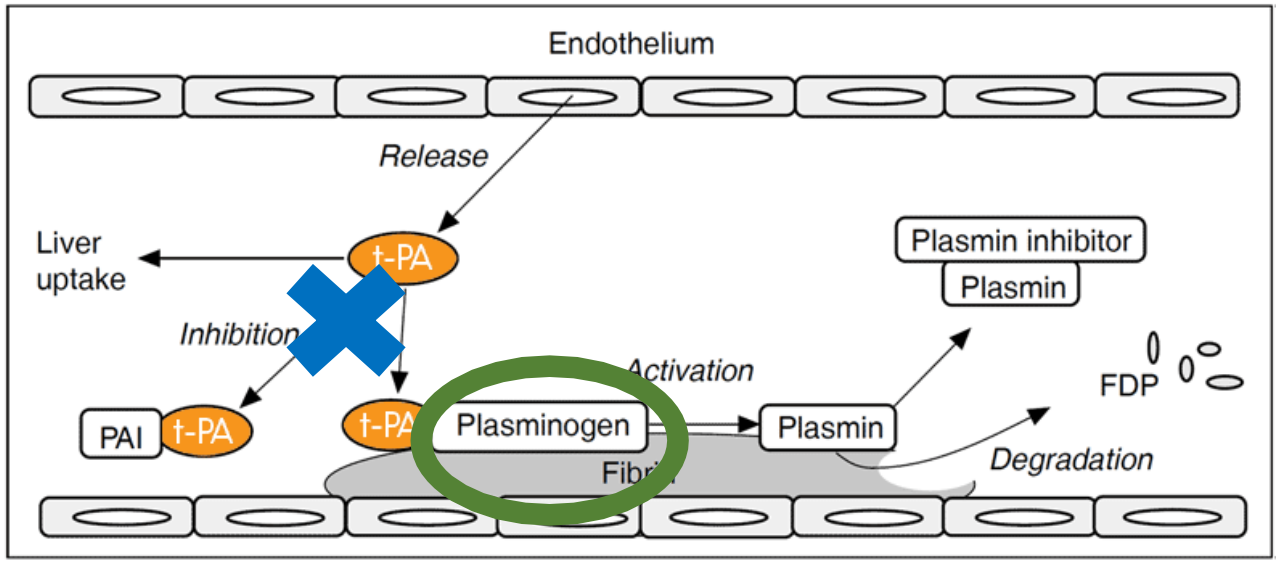
Stroke 2009; 40: 2079

Thrombolysis Frontiers



Easier Administration: Tenecteplase

- Tenecteplase (recombinant tPA)
  - More resistant to plasminogen-activator inhibitor
    - Longer half-life (22 vs 4 min)
    - Single bolus injection
  - More specific for fibrin-bound plasminogen
    - Lower risk of hemorrhage
  - Less expensive
  - Approved in US for ST-elevation MI



https://diapharma.com/tissue-plasminogen-activator-tpa/

Easier Administration: Tenecteplase

- 2019 meta-analysis (5 trials, 1585 patients)
  - 872 tenecteplase (TNK), 757 alteplase (ALT)
    - TNK 0.25 mg/kg: 24.6%, TNK 0.4 mg/kg: 68.6%
    - Largest trial utilized 0.4 mg/kg, population skewed towards minor stroke
  - Good outcome at 90 days:
    - TNK 57.9% vs ALT 55.4%
  - Conclusion: TNK is noninferior to ALT
- 2019 AHA/ASA guidelines:
  - Tenecteplase might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion. (Class IIb, Level of evidence B-R)

Powers et al. Stroke 2019;50:e344
Burgos and Saver, Stroke 2019:50:2156

Faster Treatment: Mobile Stroke Unit

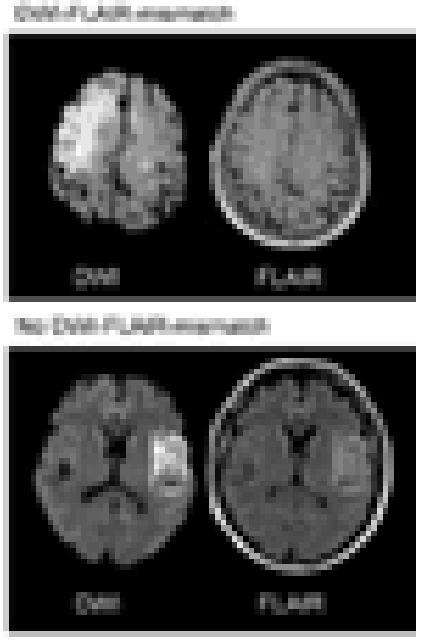
- Mobile stroke unit
  - CT scanner, point-of-care laboratory, tele-network access to physician
  - Allows diagnosis & treatment in the field

N = 100	Mobile Stroke Unit (N = 53)	Control (n= 47)
Alarm to scene	12 minutes	8 minutes
Alarm to Tx decision	35 minutes	76 minutes
Symptom to tPA	72 minutes	153 minutes

Lancet 2013;12:585

Extending Treatment Window: Imaging

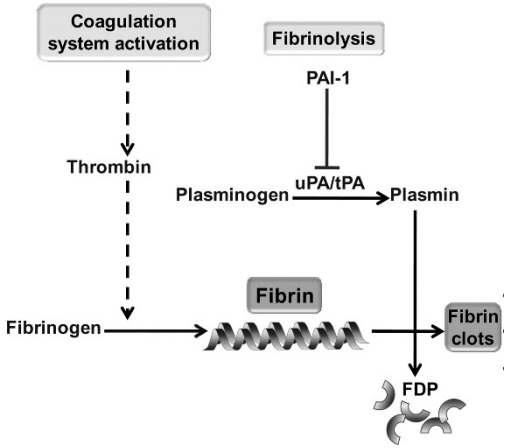
- Wake-up strokes
  - 20%-25% of strokes occur while patient is asleep
  - If “last normal” = bedtime → out of window for tPA
- WAKE-UP trial (2018)
  - MRI-based imaging to assist with stroke timing
  - Diffusion/FLAIR mismatch = stroke is eligible for treatment



Outcome	Alteplase Group (N=254)	Placebo Group (N=249)	Effect Variable	Adjusted Value (95% CI)†	P Value
Primary efficacy end point					
Favorable outcome at 90 days — no./total no. (%)‡	131/246 (53.3)	102/244 (41.8)	Odds ratio	1.61 (1.09 to 2.36)	0.02

N Engl J Med 2018; 379:611-622

Reperfusion Options



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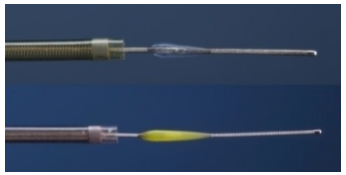
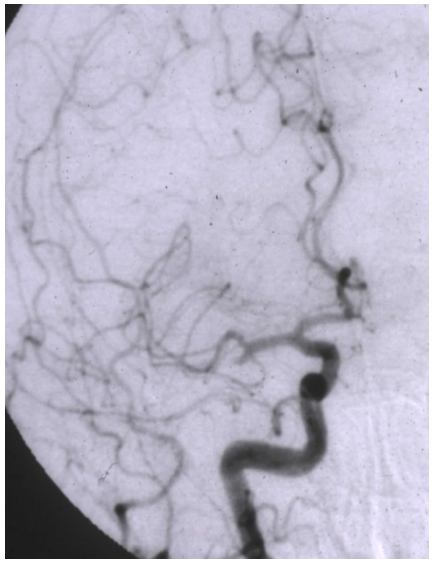
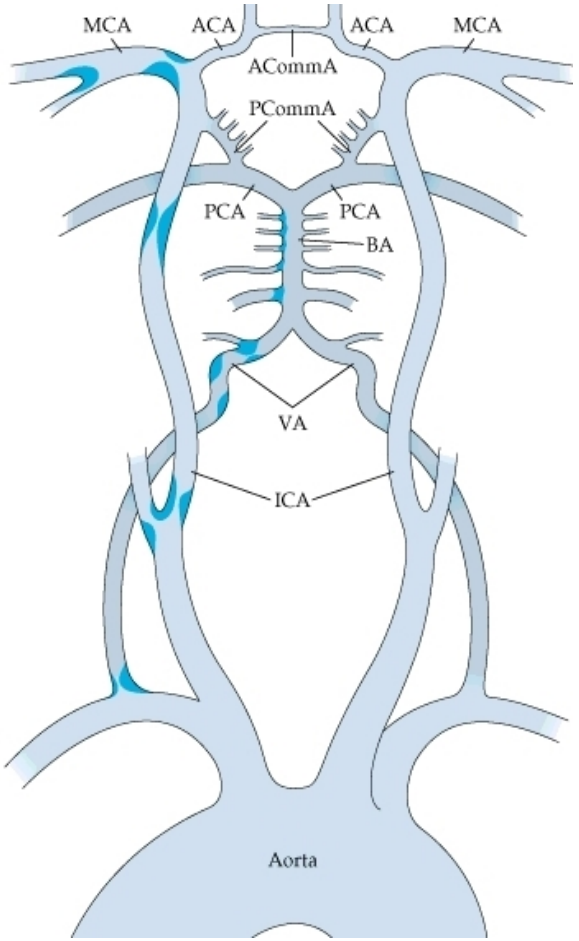




Limitations of thrombolysis: LVO (Large Vessel Occlusion)

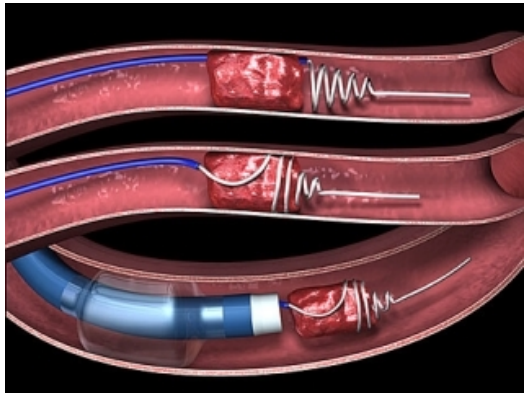
- Alteplase does not recanalize large vessels well
  - Internal carotid artery (ICA): 4%
  - Middle cerebral artery (MCA): 32%
  - Vertebral/basilar arteries: 4%
- Mortality rate is poor

Vessel	Mortality Rate
Internal carotid artery	53%
Middle cerebral artery	27%
Basilar artery	89-90%

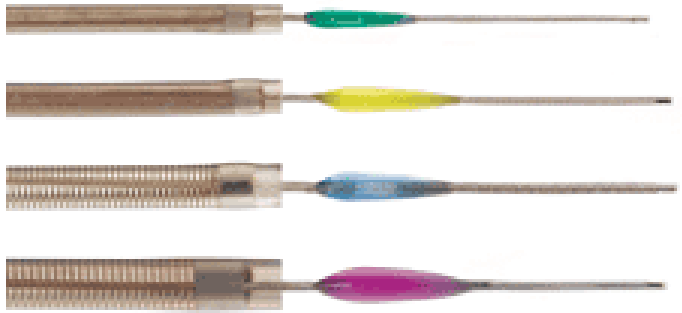


1. Jansen O, et al.
2. Furlan A et al. PROACT II Trial
3. Brückmann H et al.

Mechanical Clot Retrievers

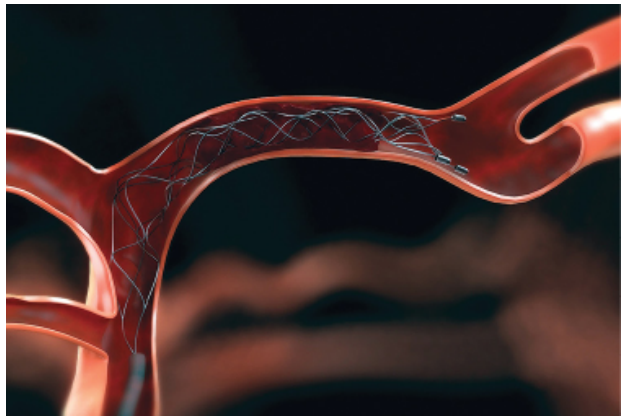


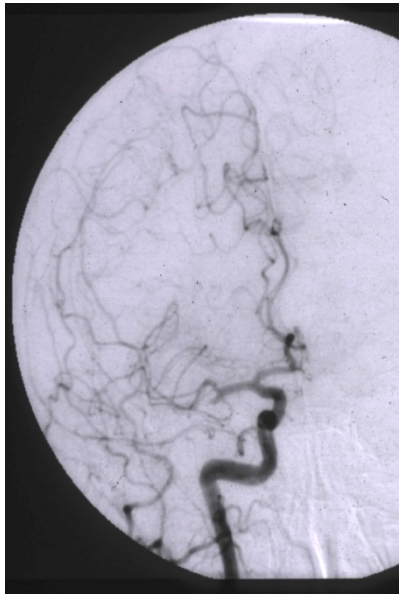
Helical coil



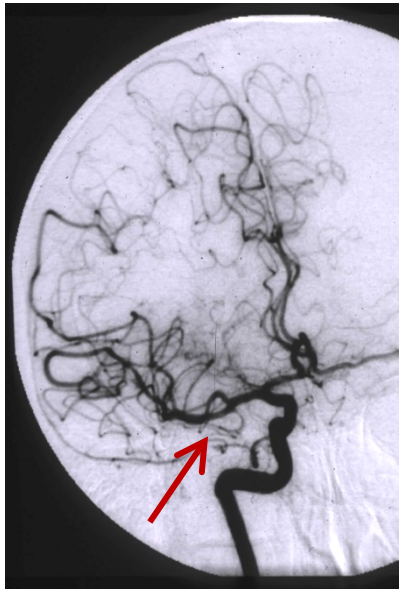
Clot aspiration

Stent retriever*





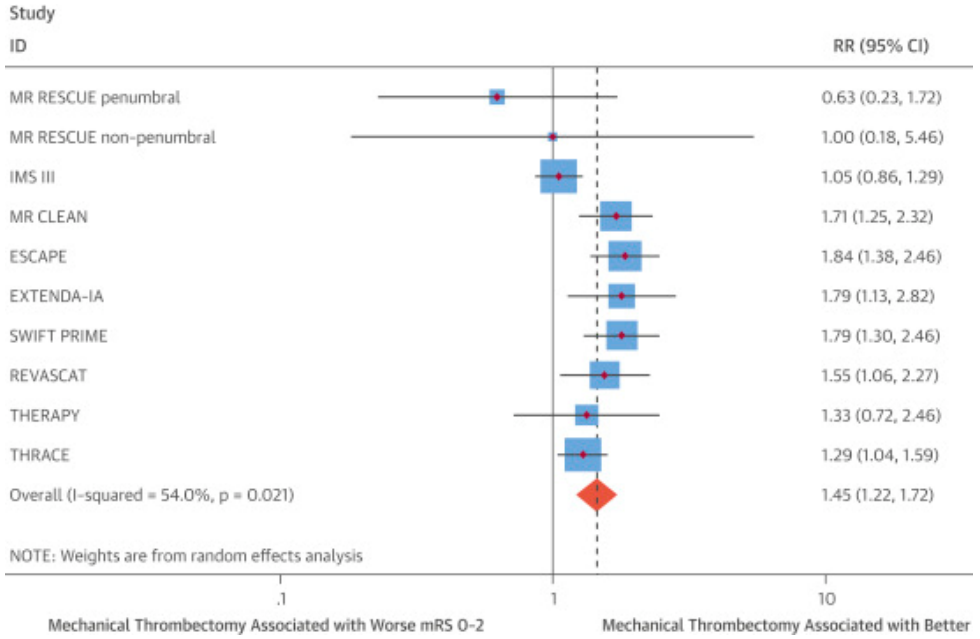
Pre-thrombectomy



Post-thrombectomy

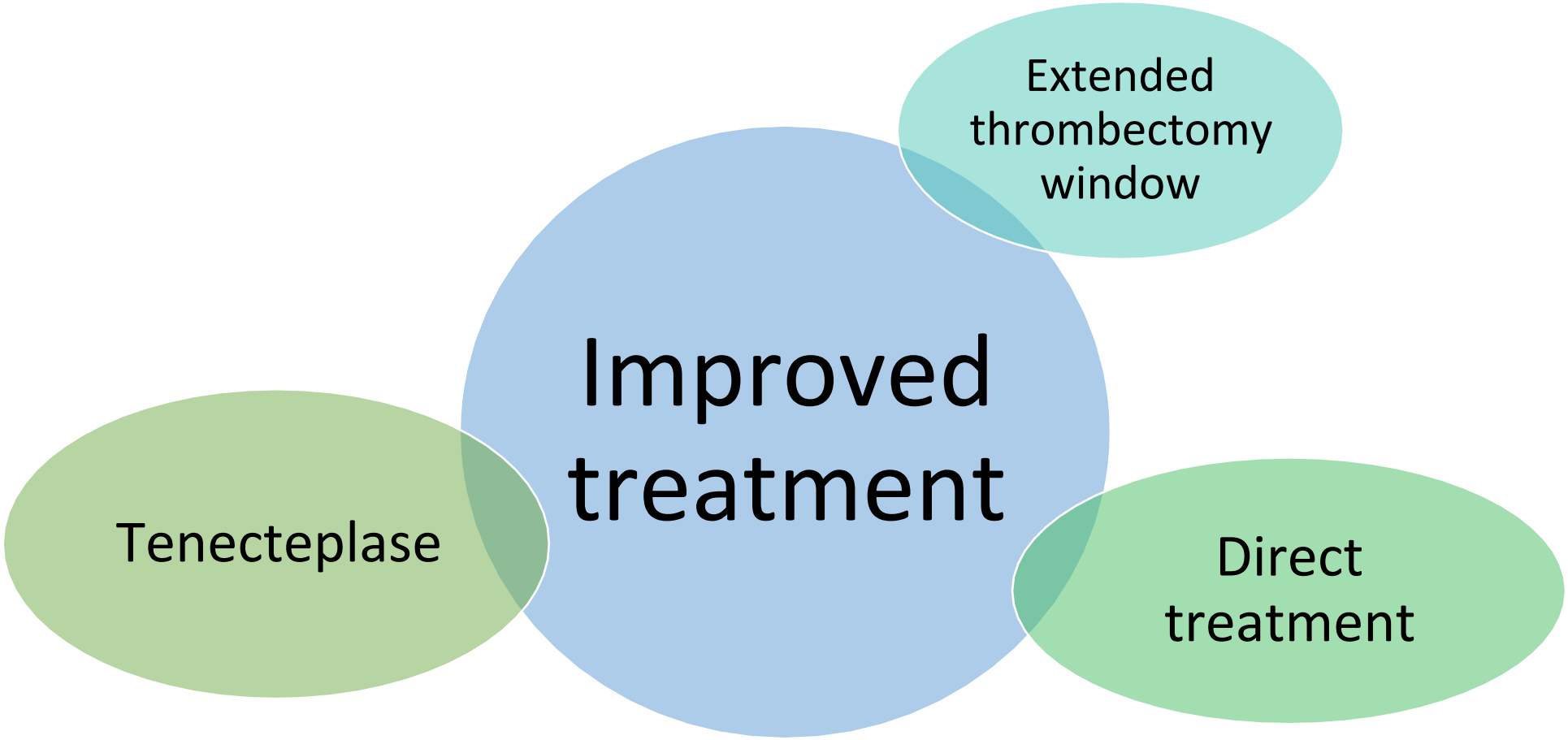
Acute Treatment: Thrombectomy

- Time-based therapy
  - Longer treatment window
  - Multiple clinical trials showing efficacy in anterior circulation up to 6 hours
- Patient selection is key
    - Large-vessel occlusion
    - Large penumbra/small core
    - Newer devices/stent retrievers
- Adjunct therapy for tPA (if eligible)
- Advantages: local effect (less systemic bleeding), more effective for large clots, longer window for intervention
- Disadvantages: personnel, technology, time

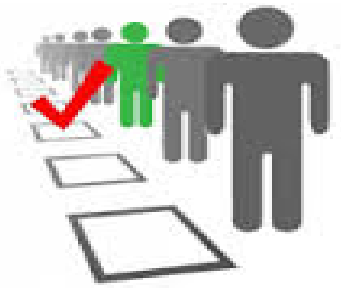


CT angiography (visualization of cerebral arteries)

LVO Frontiers

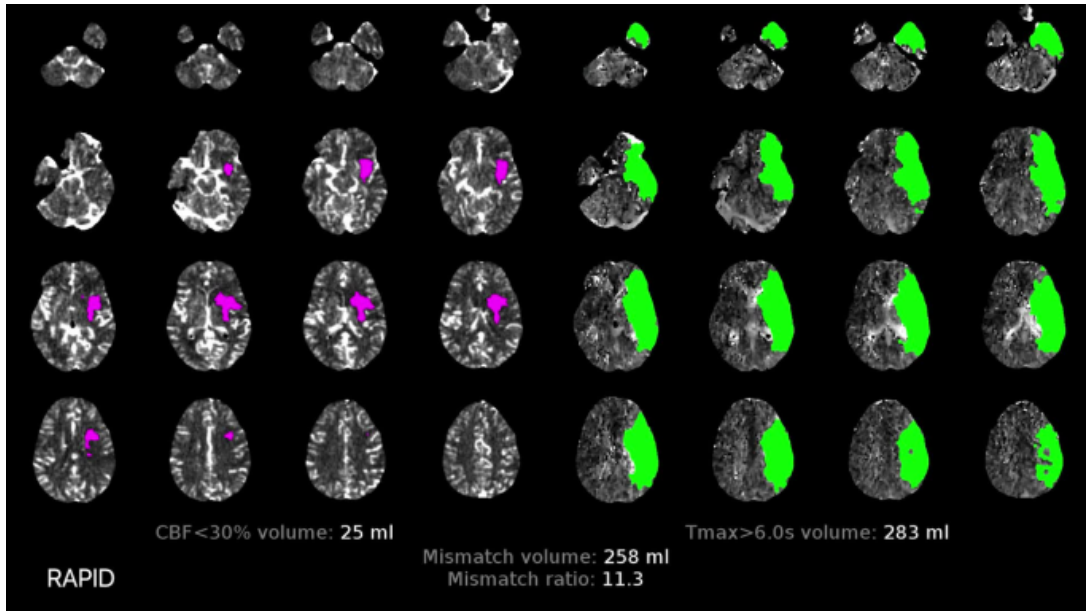


LVO Frontiers: Extended Window



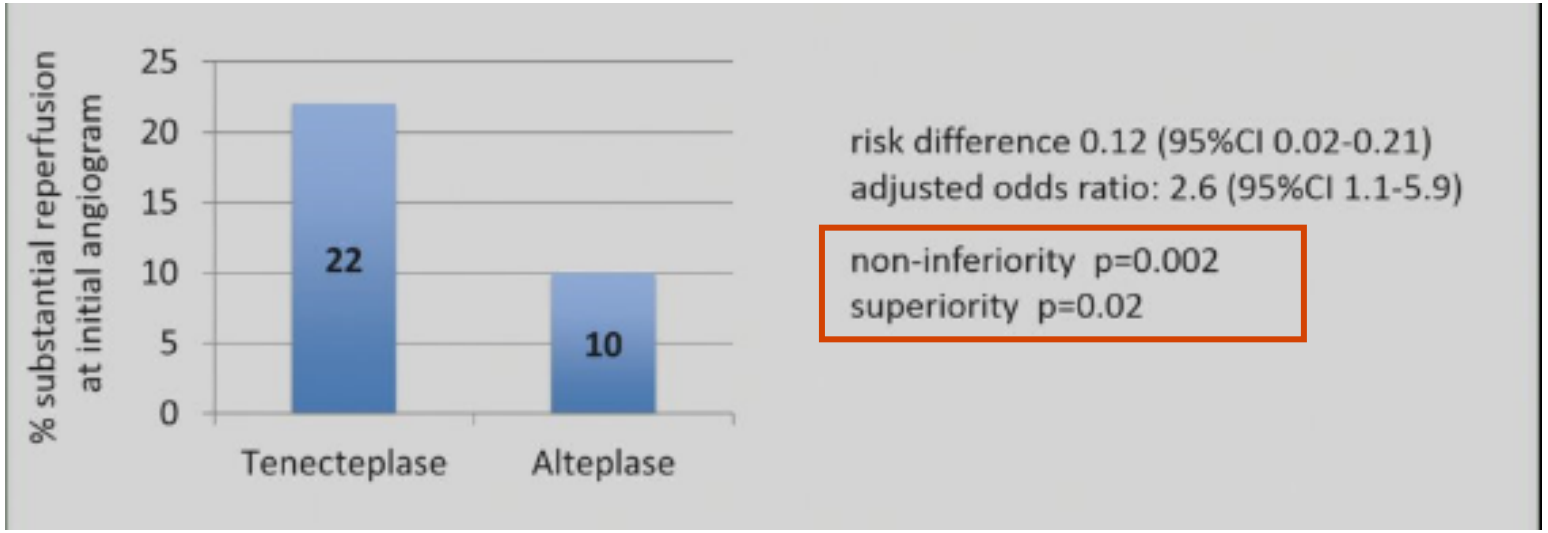
- Treatment within 6-24 hours of onset of symptoms:
  - DAWN trial (6-24h)
  - DEFUSE-3 trial (6-16h)

  - *Patient selection is key*
  - Large penumbra/small core



LVO Update: Tenecteplase

- EXTEND-IA trial 2018
  - TNK 0.25 mg/kg vs ALT 0.9 mg/kg
  - Patients with LVO who were eligible for thrombolysis and thrombectomy
  - Primary endpoint: >50% reperfusion of the involved ischemic territory, or absence of clot, prior to mechanical thrombectomy



Campbell et al. NEJM 2018;37:1573

LVO Update: Tenecteplase

- 2019 AHA/ASA guidelines: “It may be reasonable to choose tenecteplase (single IV bolus of 0.25 mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.”
  - Class IIb, Level of evidence B-R

Powers et al. Stroke 2019;50:e344.

LVO Update: Direct Treatment?

- Is it necessary to visualize the LVO before planning thrombectomy?
  - Direct to angiography suite – bypass CTA?
- Are there patients who would benefit from bypassing thrombolysis (even if they qualify) in favor of thrombectomy?
  - DIRECT-MT trial (2020)
  - SKIP trial (2021)
  - DEVT trial (2021)

N Engl J Med 2020; 382:1981-1993
JAMA. 2021;325:234-243
JAMA. 2021;325:244-253

Acute Ischemic Stroke

1. Treatment
   - Reperfusion
     - Restore cerebral blood flow
   - Supportive care
     - Minimize damage
     - Prevent complications
2. Secondary prevention
   - Prevent recurrent stroke
     - Determination of stroke cause
     - Antithrombotic therapy

Acute Post-Stroke Care

- Admission to stroke unit or neurocritical care unit
  - Benefits are comparable to those achieved with alteplase
- Keep blood pressure and volume HIGHER
  - Hold antihypertensives
  - Tolerate SBP<220, DBP<120
  - IV fluids (NSS)
- Normalize glucose
- Normalize temperature
- Prevent aspiration
- Prevent venous blood clots

Acute Ischemic Stroke

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   - Reperfusion
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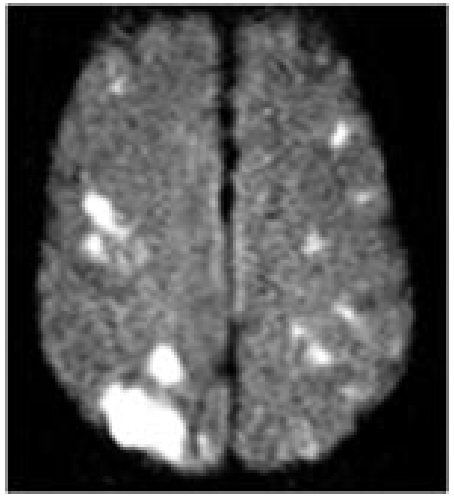
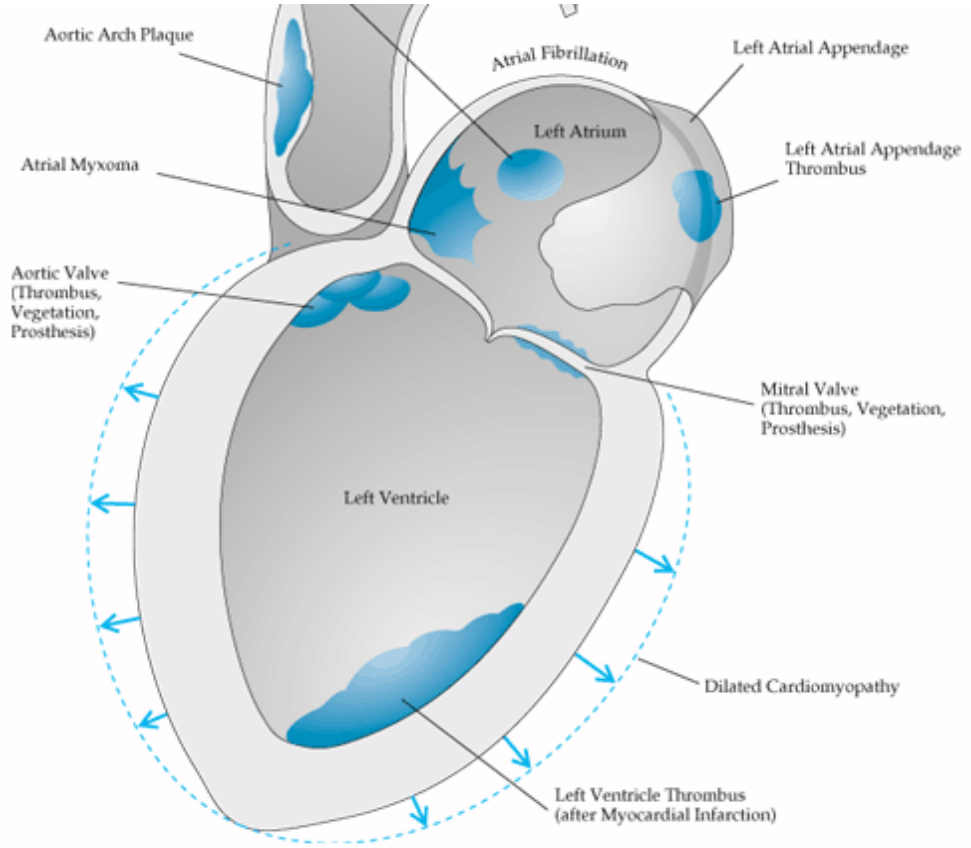
Classification of Ischemic Stroke: Underlying Causes

1. Cardioembolism
2. Large vessel atherosclerosis
3. Small vessel disease
4. Rare causes of stroke
5. Cryptogenic/idiopathic

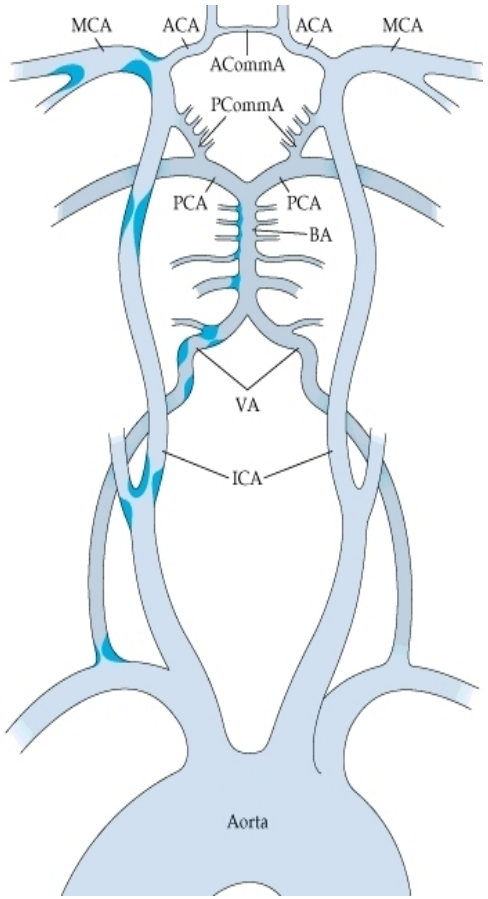
Cardioembolism



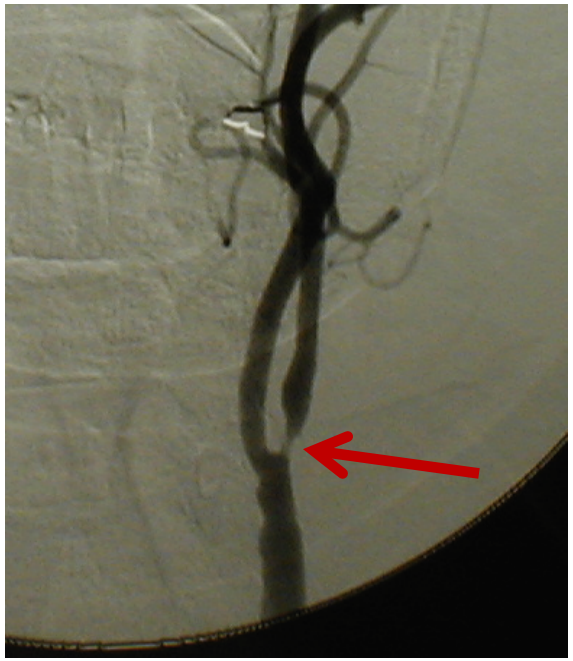
- ~20% of ischemic strokes
- Suspect:
  - Multiple vascular territories
  - Concomitant systemic emboli
  - Cortical strokes
- Common causes:
  - Atrial arrhythmias - atrial fibrillation/flutter*
  - Left heart structural abnormalities
    - LV mural thrombus
    - Congestive heart failure
    - Left atrial appendage thrombus
    - Cardiac tumors
  - Valvular disease
    - Prosthetic valves
    - Endocarditis
      - Infectious
      - Marantic



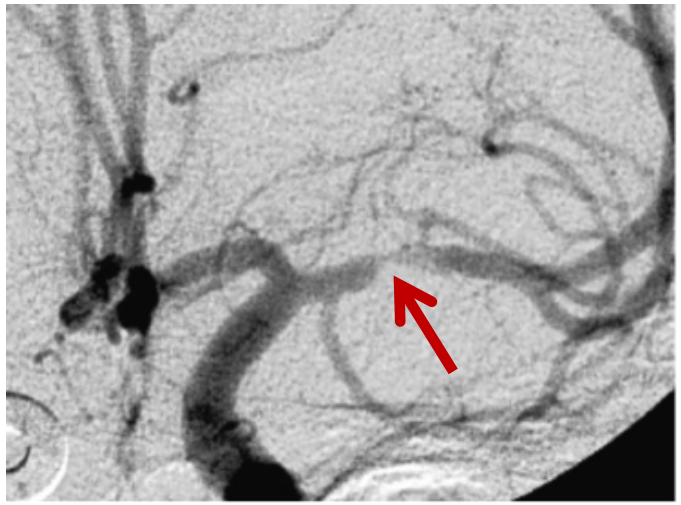
Large Artery Atherosclerosis

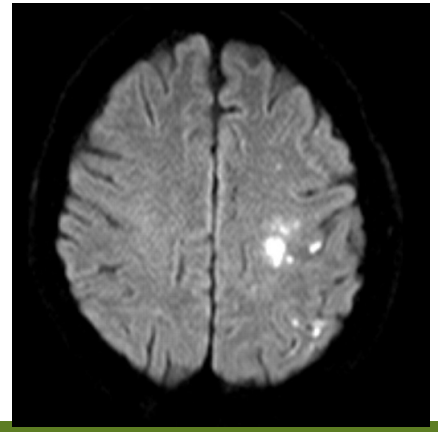


Extracranial ICA disease



Intracranial MCA disease



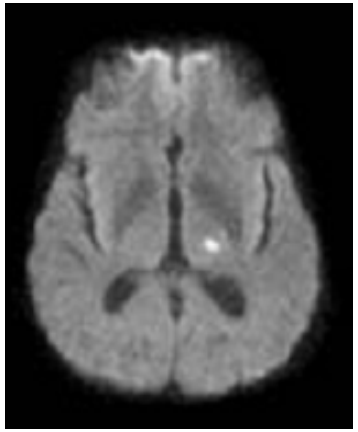


~15% of strokes

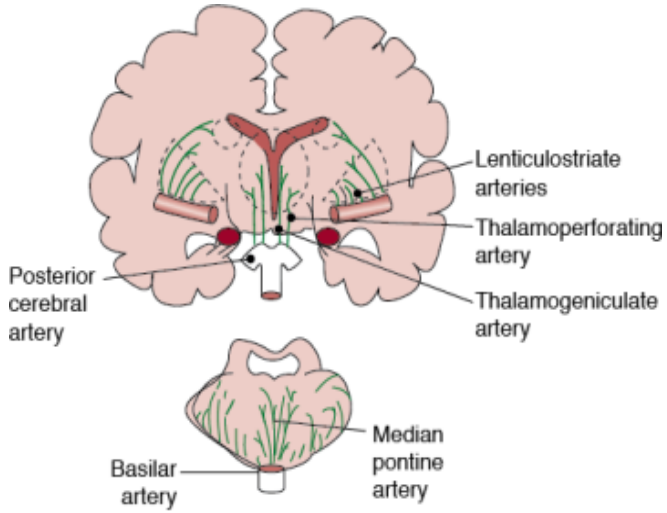
Stroke due to:

- Artery-artery embolism
- Hypoperfusion

Small Vessel Disease



- ~25% of all ischemic strokes
- Requires:
  - Subcortical location:
    - Internal capsule, basal ganglia, thalamus
  - <15 mm in size
- Small-vessel lipohyalinosis/ microatheroma
- Many lacunes are clinically silent



Rare Causes of Ischemic Stroke (~5%)

- Carotid/vertebral artery dissection
- Vasculopathy
  - Cocaine
  - Migraine
  - Vasculitis
- Genetic
  - Sickle cell disease
  - Fabry's disease
  - CADASIL
- Hypercoagulable states
  - Cancer
  - Infections (Covid-19)
  - Antiphospholipid antibodies
  - Factor V Leiden
  - Prothrombin mutation
  - Protein C, S, antithrombin III deficiency
- Paradoxical embolism
  - Patent foramen ovale
- Pregnancy, oral contraceptives, HRT

Causes of Ischemic Stroke

1. Cardioembolism
2. Large vessel atherosclerosis
3. Small vessel disease
4. Rare causes of stroke
5. **Cryptogenic/idiopathic**
   - Cause is not determined – diagnosis of exclusion
   - 20%-30% of all strokes
   - Embolic stroke of undetermined source (ESUS)

Panel 2: Criteria for diagnosis of embolic stroke of undetermined source*

- Stroke detected by CT or MRI that is not lacunar†
- Absence of extracranial or intracranial atherosclerosis causing ≥50% luminal stenosis in arteries supplying the area of ischaemia
- No major-risk cardioembolic source of embolism‡
- No other specific cause of stroke identified (eg, arteritis, dissection, migraine/vasospasm, drug misuse)

Panel 3: Proposed diagnostic assessment for embolic stroke of undetermined source*

- Brain CT or MRI
- 12-lead ECG
- Precordial echocardiography
- Cardiac monitoring for ≥24 h with automated rhythm detection†
- Imaging of both the extracranial and intracranial arteries supplying the area of brain ischaemia (catheter, MR, or CT angiography, or cervical duplex plus transcranial doppler ultrasonography)

*Imaging of the proximal aortic arch is not needed; special blood tests for prothrombotic states only if the patient has a personal or family history of unusual thrombosis or associated systematic signs or disorder. †Cardiac telemetry is not sufficient.

Lancet Neurol 2014;13:429-438

Secondary Stroke Prevention

1. Vascular risk factor modification
    - Antihypertensives, goal BP <130/80 in long term
    - Cholesterol-lowering therapy
        - Statin
        - Ezetimibe
        - PSCK9 inhibitors
    - Glycemic control
    - Diet, physical activity, smoking cessation counseling
    - Stroke symptom education

Secondary Stroke Prevention

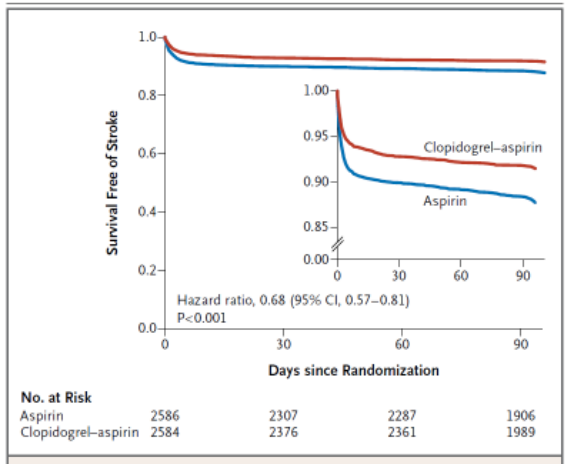
2. Antithrombotic treatment
    - WHO
        - Patient characteristics?
    - WHAT
        - Antiplatelet vs anticoagulation?
    - WHEN
        - How long since the stroke?
    - WHERE
        - How large is the stroke?
    - WHY
        - Underlying stroke mechanism?

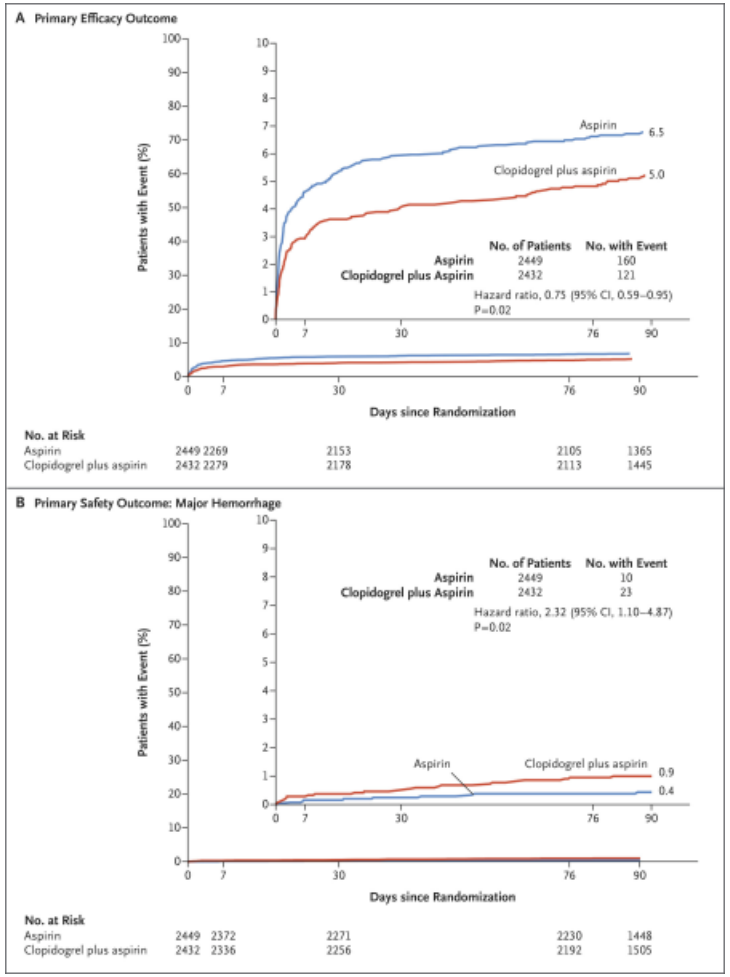
Acute Treatment (<48h)

- Antiplatelet
  - Aspirin monotherapy is gold standard
    - Joint Commission metric - administered within 48 hours
  - Other antiplatelets? (clopidogrel, cilostazol, dipyridamole, ticagrelor)
    - No data
    - *Patients already on aspirin?*
- Anticoagulation is generally not indicated for most patients in the short term
  - Risk of hemorrhagic transformation of stroke outweighs benefit
  - Consider for select patients
    - High risk of recurrent cardioembolic stroke (mechanical valve, visualized LV thrombus)
    - Other life-threatening medical condition that requires anticoagulation (ACS, DVT/PE, etc)
    - Small infarct/TIA

Update: Short-Term Dual Antiplatelets

- Dual antiplatelet therapy (aspirin + clopidogrel)
  - Minor stroke (NIHSS ≤3) or high-risk TIA (ABCD2 score ≥4)
    - CHANCE, POINT trials
  - 21 days, then transition to antiplatelet monotherapy long-term





N Engl J Med 2013; 369:11-19
N Engl J Med 2018; 379:215-225

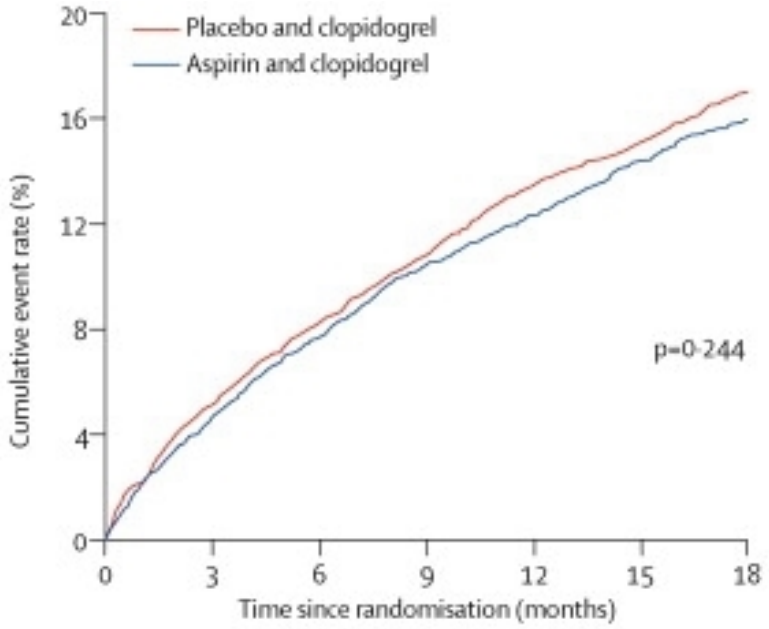
Long-Term Treatment

- Choice of treatment is specific to mechanism
- Long term:
  - Antiplatelet agents:
    - Large artery atherosclerosis
    - Small vessel disease
    - Cryptogenic stroke/ESUS
  - Anticoagulation:
    - Cardioembolic stroke
    - Hypercoagulable states

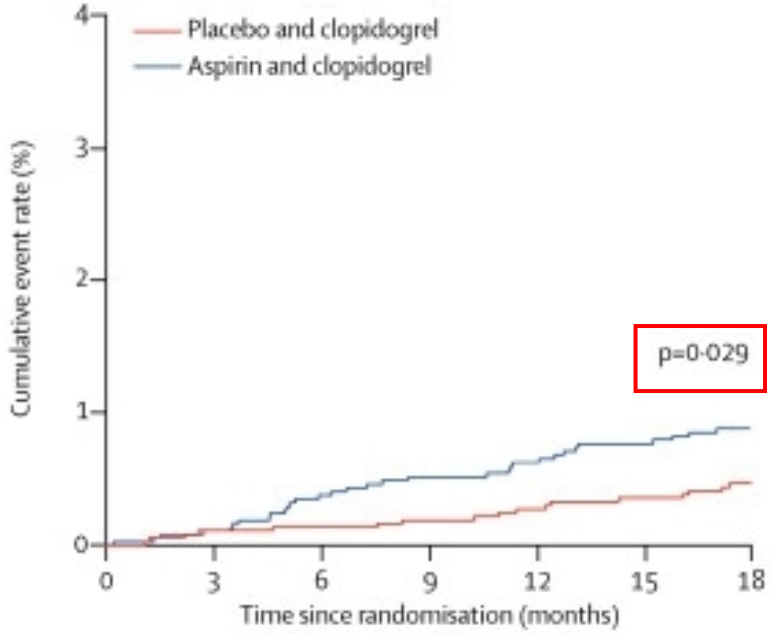
Long-Term Treatment

- No role for *long-term* dual antiplatelet therapy (DAPT)
  - Increased risk of hemorrhage outweighs stroke prevention benefit
  - If a patient is discharged on short-term DAPT from the hospital, they should not be continued indefinitely!

Efficacy (composite vascular events)



Safety (intracranial hemorrhage)

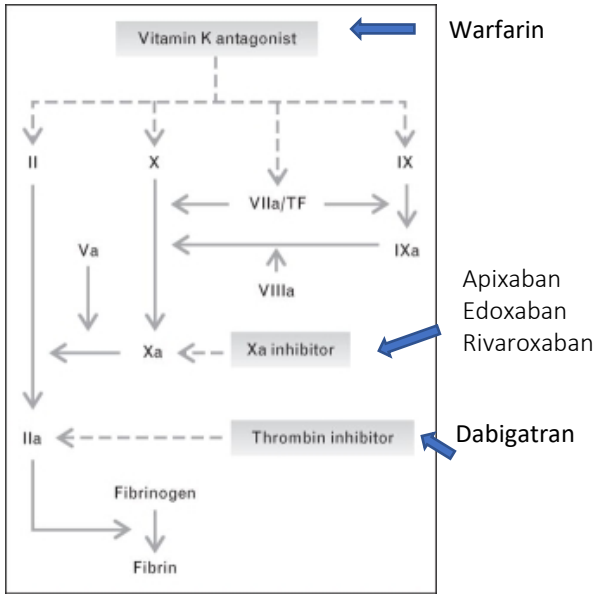


Lancet. 2004;364:331-337.

Specific Recommendations

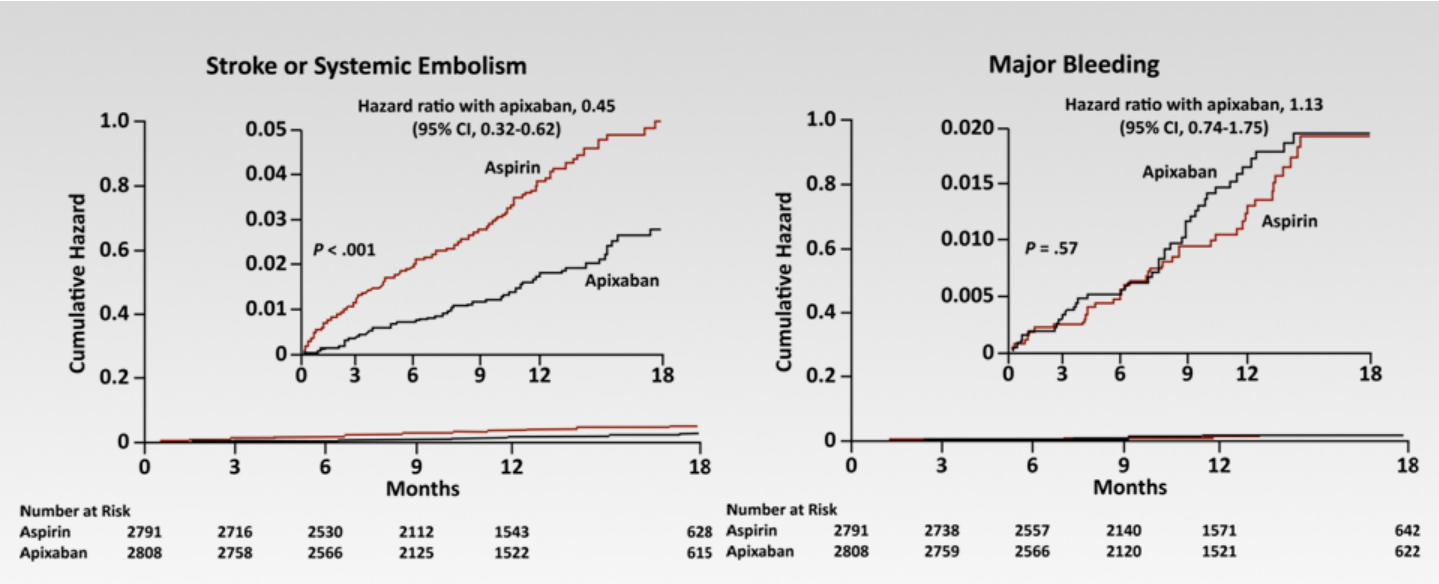
- Atrial fibrillation
- Carotid stenosis
- High-grade intracranial atherosclerosis
- Patent foramen ovale (PFO)
- Embolic stroke of undetermined source (ESUS)

Secondary Prevention: Atrial Fibrillation



- Warfarin
- Direct oral anticoagulants
  - Direct thrombin inhibitor
  - Factor Xa inhibitors
- When to start after stroke?
  - Decision made on basis of stroke size, stroke location, and risk of recurrent embolic event
    - Risk of recurrent stroke with Afib estimated at 5% over 2-4 wks
    - Visualized LV thrombus?
  - General guidelines:
    - Start immediately for TIA
    - Wait 3-5 days for small/med strokes (<1/3 MCA territory)
    - Wait 7-14 days for larger strokes
  - Factor in time to therapeutic benefit
  - Warfarin: 3-5 days
  - DOACs: immediate

Patients “Unsuitable” for Warfarin?



AVERROES trial:

AF + 1 additional stroke RF, deemed unsuitable for warfarin per enrolling physician

Apixaban 5 mg BID vs ASA (100-325 mg)

All strokes: ARR 1.8 per year (p<0.001)

Major bleed: no significant difference

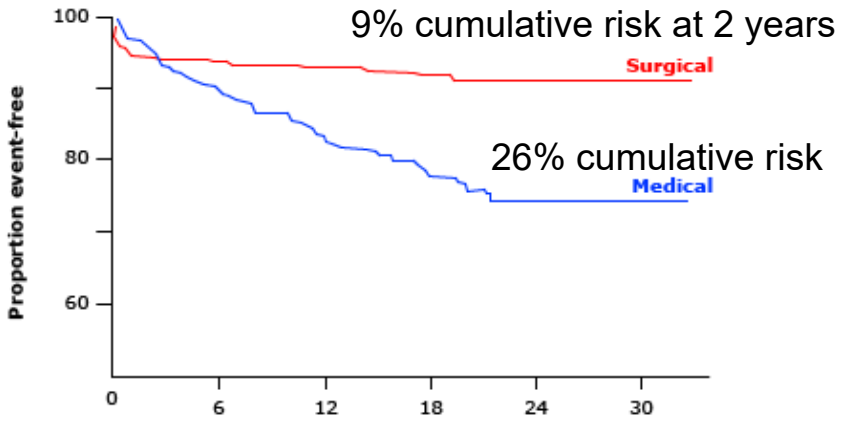
“Fall risk”:

Patient must fall several times per WEEK for risk of warfarin to outweigh benefit

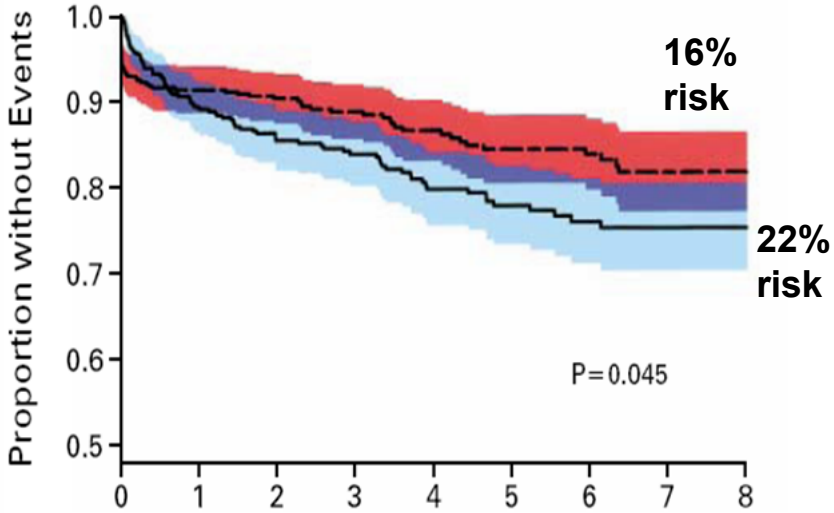
N Engl J Med 2011; 364:806
Arch Intern Med 1999;159:677

Secondary Prevention: Extracranial Carotid Stenosis

- Cervical carotid endarterectomy
  - Consider if “symptomatic” – downstream stroke
  - Benefit depends on degree of stenosis
    - High-grade stenosis (70%-99%): clear benefit to surgery
    - Moderate stenosis (50%-69%): select patients
    - No benefit for patients with stenosis <50%
  - Other considerations:
    - Highest benefit with early intervention (within 2 weeks of stroke)
    - Men benefit more than women
    - Older patients benefit more than younger
    - Caveat: medical management has evolved since trials



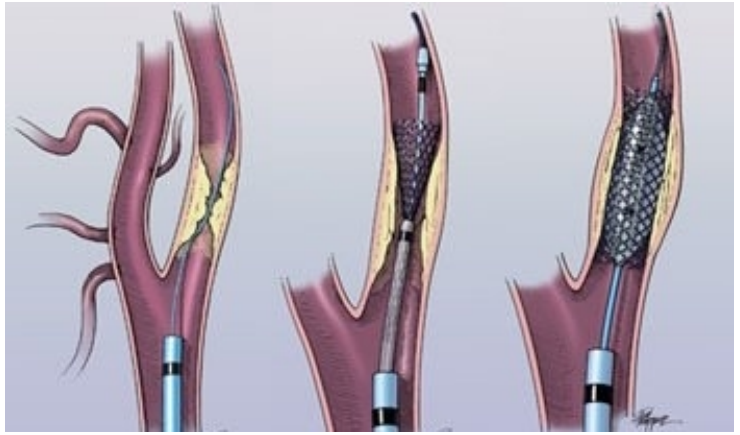
Any Ipsilateral Stroke, 50–69% Stenosis



NEJM. 1991; 325:445

Secondary Prevention: Extracranial Carotid Stenosis

- Carotid stenting
  - Endarterectomy is superior for most patients
    - 30-day stroke/death rate with stenting is higher than CEA (8.2% vs 5.0%, OR 1.72, 95% CI 1.29-2.31)
    - Lower risk of MI (OR 0.44)
    - CREST trial: Age >70 favors CEA
  - Consider stenting in certain patients:
    - Recurrent stenosis after CEA
    - Surgically-inaccessible disease
      - Above C2 or below clavicle
    - Post-radiation stenosis
    - Poor operative candidates
      - Severe CHF, angina, recent MI, chronic lung disease



N Engl J Med. 2010;363(1):11

Secondary Prevention: Intracranial Atherosclerosis

- Short-term dual antiplatelets (90 days)
  - SAMMPRIS trial*
    - Patients with stroke secondary to high-grade intracranial atherosclerosis
    - “Aggressive medical management” vs intracranial stent
      - Aspirin 325 mg daily + clopidogrel 75 mg for 90 days
      - Aggressive vascular risk factor control
    - Conclusion: medical management superior to stenting
    - Compared to historical controls with antiplatelet monotherapy (ie, not a true randomized controlled trial):
      - 30-day stroke/death: 5.8% vs 10.7%
      - 1-year stroke/death: 12.2% vs 25%
    - DAPT for 90 days has become standard of care, then transition to antiplatelet monotherapy

N Engl J Med. 2011;365:993
Lancet 2014: 383:333-341

Secondary Stroke Prevention: PFO

TABLE 1. RoPE SCORE CALCULATOR		
Characteristic	**Points**	**Score**
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age (y)		
18–29	5	
30–39	4	
40–49	3	
50–59	2	
60–69	1	
≥ 70	0	
Total score (sum of individual points)		
Maximum score (a patient < 30 y without vascular risk factors, no history of stroke or TIA, and cortical infarct)		10
Minimum score (a patient ≥ 70 y with vascular risk factors, prior stroke, and no cortical infarct)		0

Is the PFO causative of stroke?

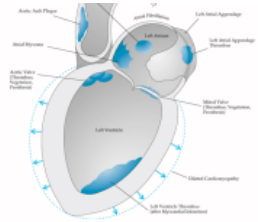
Table 5 PFO prevalence, attributable fraction, and estimated 2-year risk of stroke/TIA by point score strata, using control rate of 25%

	Cryptogenic stroke (n = 3,023)			CS patients with PFO (n = 1,324)	
RoPE score	No. of patients	Prevalence of patients with a PFO, % (95% CI)[a]	PFO-attributable fraction, % (95% CI)[a]	No. of CS patients with PFO[a]	Estimated 2-y stroke/TIA recurrence rate (Kaplan-Meier), % (95% CI)
0-3	613	23 (19-26)	0 (0-4)	108	20 (12-28)
4	511	35 (31-39)	38 (25-48)	148	12 (6-18)
5	516	34 (30-38)	34 (21-45)	186	7 (3-11)
6	482	47 (42-51)	62 (54-68)	236	8 (4-12)
7	434	54 (49-59)	72 (66-76)	263	6 (2-10)
8	287	67 (62-73)	84 (79-87)	233	6 (2-10)
9-10	180	73 (66-79)	88 (83-91)	150	2 (0-4)

Abbreviations: CI = confidence interval; CS = cryptogenic stroke; PFO = patent foramen ovale; RoPE = Risk of Paradoxical Embolism.
[a] Note: 95% CI for PFO prevalence and attributable fraction based on normal approximation to the binomial distribution.

Neurology. 2013; 81: 619–625.

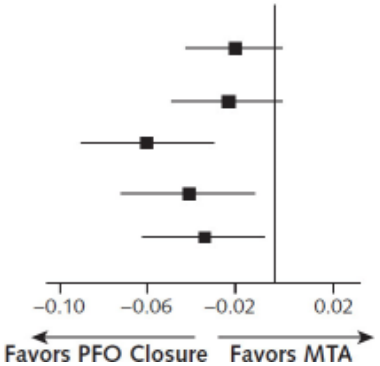
Secondary Prevention: PFO



- Percutaneous closure
  - Consider for select patients
    - <60 years old
    - Patient has undergone workup for alternate cause of stroke
    - PFO is felt to be causative of stroke
- Concomitant antiplatelet
  - Anticoagulation for DVT

Study, Year (Reference)	Events/Patients, *n*/*n*		Risk Difference	Risk Difference (95% CI)
	Device Closure	MTA		
PC, 2013 (7)	1/204	5/210	−0.019	
RESPECT extended, 2017 (12)	18/499	28/481	−0.022	
CLOSE, 2017 (10)	0/238	14/235	−0.060	
REDUCE, 2017 (11)	6/441	12/223	−0.040	
Total	25/1382	59/1149	−0.033	

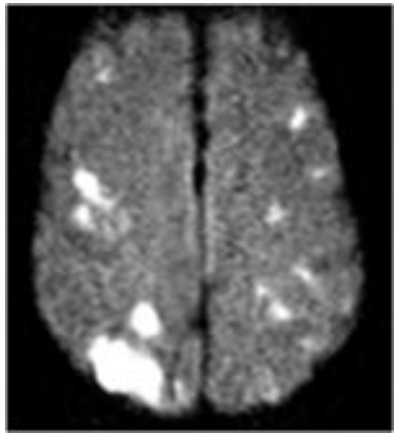
Heterogeneity: $Q = 5.06$; $P = 0.16$; $I^2 = 40.74\%$



Ann Int Med 2018;168:335

Secondary Stroke Prevention: ESUS

- Multiple clinical trials have failed to show a benefit for anticoagulation
  - RESPECT-ESUS: dabigatran vs aspirin
  - Navigate-ESUS: rivaroxaban vs aspirin
- Current standard: antiplatelet therapy
- Ongoing clinical trial assessing apixaban vs aspirin in patients with ESUS and high -risk cardiac features (Arcadia)



N Engl J Med 2018; 378:2191-2201

N Engl J Med 2019; 380:1906-1917

Summary

- Treatment
  - Thrombolysis
    - Alteplase remains the gold standard for treatment of acute ischemic stroke with disabling symptoms within 4.5h of onset
    - Frontiers: tenecteplase, extended window, faster treatment
  - Thrombectomy
    - Standard of care for patients with large-vessel occlusion, salvageable penumbra <6 hours
      - Select patients with very small core in extended window (6-24h)
- Secondary prevention (antithrombotics)
  - Short-term: aspirin
    - 21-day aspirin plus clopidogrel for minor stroke or high-risk TIA
  - Long-term: antiplatelet or anticoagulation, depending on stroke mechanism

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